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Allergenic Potency of Spices: Hot, Medium Hot, or Very Hot

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Spices · Allergy · Food allergy · Cross-reactivity

Abstract
Spices are the most attractive ingredients to confer an authentic taste to food. As they are derived from plants, they harbour allergenic potency and can induce symptoms ranging from mild local to severe systemic reactions. Due to the content of pharmacologically active substances of spices, the diagnosis of allergy and the differentiation from intolerance reactions may be difficult. Association with inhalative allergies via IgE cross-reactivity, but also direct gastrointestinal sensitization plays a role. This article is a botanical and allergological overview of the most important spices and molecules responsible for eliciting IgE-mediated reactions or cross-reactions. As no curative treatments are known at present, strict avoidance is recommended and, therefore, accurate labelling of pre-packed food is necessary.

Spices and Blends

Spices have always belonged to the most precious goods of mankind, and several families have built up empires on spice trade. During the spice war on the Spice Islands in Eastern Indonesia in the 16th century, some 6,000 people were killed. 'Private wars' are still going on between and in families dealing with spices, as for instance in the Pathak dynasty, which was settled only recently (www.thehindu.com). However, besides their undoubtedly attractive properties, spices may also lead to food allergy. An overview of the botanical families and the overall allergenicity of spices is given in table 1, and reported IgE reactivities to identified and yet unidentified molecules, or extracts of spices are listed in detail in table 2. Spices without yet reported allergenic potential are listed as well and may provide the affected patients and their physicians with information about alternatives to season and flavour food. The botanical relations are depicted in figure 1. As spice blends can consist of many different kinds, we also provide examples of the composition of the most common blends in table 3. However, the contents of these blends may vary depending on locally available spices, on geographic tradition or on manufacturer's recipes. Additionally, such compositions can contain sources of allergens other than the contained spices, e.g. tomatoes [1] in ketchup, soybean oil [2] or starch [3] contained in several mixtures. Useful internet pages are listed in table 4.

Who Is Affected by Spice Allergy?

Among all food allergies, which affect 2% of the adult population in the industrialized world, spice allergy represents only another 2% of these cases. Women have a twofold risk to develop food allergies including spices, due to unknown reasons [4, 5]. Spice allergy is a problem of adults and is seen frequently in children [6]. However, dietary preferences may influence whether children are also affected, as shown by sesame allergy in Israel [7]. Spice hypersensitivity may represent a factor aggravating the atopic syndrome in young children; vice versa, avoiding spice consumption can lead to an improvement of

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Table 1. Botanical families and reports of allergenicity of spices

Spices (synonyms)	Species	Family	Reported symptoms	Allergy reports
Allspice (Jamaica pepper, myrtle pepper, newspice, pimento)	*Pimenta dioica*	*Myrtaceae*	contact dermatitis	[31, 40]
Anise (anis, anise, aniseed, sweet cumin)	*Pimpinella anisum*	*Apiaceae* = *Umbelliferae*	rhinoconjunctivitis, food allergy, contact urticaria, delayed type allergy	[12, 16, 47, 57, 87–91]
Basil (basilie, herb of kings, sweet basil, tomato herb)	*Ocimum basilicum*	*Lamiaceae* = *Labiatae*	contact dermatitis	[60, 85, 92, 93]
Bay leaf (laurel, sweet bay)	*Laurus nobilis*	*Lauraceae*	perioral dermatitis, contact dermatitis, asthma	[42, 94–96]
Caraway seed (caraway, carvies, wild cumin)	*Carum carvi*	*Apiaceae*	rhinoconjunctivitis, gastrointestinal syndromes	[12]
Cardamom (black c., brown c., greater Indian c., Nepal c.) (green c.)	*Amomum subulatum* *Elettaria cardamomum*	*Zingiberaceae*	skin symptoms	[17, 97]
Cayenne (chili pepper, red pepper)	*Capsicum frutescens*	*Solanaceae*		see chilli
Celery (celeriac)	*Apium graveolens*	*Apiaceae*	anaphylactic reactions	[56, 98–100], reviewed e.g. in [101]
Chervil (French parsley, garden chervil)	*Anthriscus cerefolium*	*Apiaceae*		–
Chilli (cayenne, red pepper)	*Capsicum baccatum* *Capsicum chinense* *Capsicum frutescens* *Capsicum pubescens*	*Solanaceae*	respiratory symptoms, generalized eczema	[9, 102, 103]
Chives	*Allium schoenoprasum*	*Alliaceae*	contact dermatitis	[104]
Cinnamon (Barbasco, canella, white c., wild c.) (fagot cassia, Indonesian c., Jawa cassia, Padang c.) (cassia, bastard c., Chinese c.) (Vietnamese c., Saigon c.) (Sri Lanka c., Ceylon c., c. buds)	*Canella winteriana* *Canella alba* *Cinnamomum burmannii* *Cinnamomum cassia* *Cinnamomum loureirii* *Cinnamomum verum* *Cinnamomium zeylanicum*	*Canellaceae* Lauraceae	respiratory symptoms, rhinoconjunctivitis, contact dermatitis, stomatitis, delayed type allergy	[9, 12, 17, 22, 31, 35, 40, 69, 85, 94, 97, 105–121]
Cloves	*Syzygium aromaticum*	*Myrtaceae*	contact dermatitis	[22, 31, 35, 118, 120, 121]
Coriander (Cilantro, Chinese parsley, Indian parsley) (Vietnamese C.)	*Coriandrum sativum* *Polygonum odoratum*	*Apiaceae* *Polygonaceae*	asthma, contact allergy, anaphylaxis	[9, 12, 22, 27, 47, 62, 63, 69, 82, 83, 85, 87, 122, 123]
Cumin seeds (black C.) (green C., white C.)	 *Bunium persicum* *Cuminum cyminum*	 *Apiaceae*	 anaphylaxis, contact dermatitis	 (12, 16, 47, 69, 124)
Dill	*Anethum graveolens*	*Apiaceae*	anaphylaxis, contact urticaria	[12, 29, 87, 125–127]
Fennel (sweet cumin)	*Foeniculum vulgare*	*Apiaceae*	rhinoconjunctivits, asthma, atopic dermatitis	[12, 20, 47, 54, 57, 69, 103, 128–133]

Table 1 (continued)

Spices (synonyms)	Species	Family	Reported symptoms	Allergy reports
Garlic	*Allium sativum*	*Alliaceae*	contact dermatitis, asthma, rhinitis, anaphylaxis	[20, 134–160]
Ginger	*Zingiber officinale*	*Zingiberaceae*	contact dermatitis, respiratory symptoms	[6, 9, 31, 63, 69, 85, 87]
Jalapeno pepper	*Capsicum annuum*	*Solanaceae*		see chilli
Lovage (garden lovage, bladder seed, love parsley)	*Levisticum officinale*	*Apiaceae*		–
Mace	*Myristica fragrans*	*Myristicaceae*		see nutmeg
Marjoram (sweet m., knotted m.)	*Maiorana hortensis*	*Lamiaceae*	perioral dermatitis, atopic eczema	[93, 94, 161, 162]
Mustard (black m., brown m., Indian m., oriental m.) (white m.)	*Brassica nigra* *Brassica juncea* *Sinapis alba*	*Myrtaceae* *Brassicaceae*	anaphylaxis, delayed type reaction, contact urticaria	[23, 25, 83, 63–183]
Nutmeg, mace	*Myristica fragrans*	*Myristicaceae*	asthma, contact allergy	[6, 9, 14, 22, 42, 62, 63, 69, 85, 96, 97, 184, 185]
Onion (scallion, shallots)	*Allium cepa*	*Alliaceae*	contact allergy, anaphylaxis, asthma, rhinoconjunctivitis	[142, 153, 186–195]
Oregano (wild marjoram, oregan)	*Origanum vulgare*	*Lamiaceae*	systemic reactions	[85, 93, 96, 162]
Paprika (bell pepper, pod pepper, sweet pepper)	*Capsicum annuum*	*Solanaceae*	contact urticaria, rhinoconjunctivitis	[9, 19, 22, 30, 42, 44, 45, 63, 70–72, 83, 196–202]
Parsley	*Petroselinum crispum*	*Apiaceae*	angioedema, urticaria	[54, 153, 203–206]
Pepper (black p., white p., green p.)	*Piper nigrum*	*Piperaceae*	respiratory symptoms, contact dermatitis	[9, 11, 17, 22, 42, 44, 45, 62, 69, 71, 72, 82, 196, 199, 202, 207–209]
Pink peppercorns (Brazil p., pepper rosé) (Peruvian P.)	*Schinus terebinthifolius* *Schinus molle*	*Anacardiaceae*	atopic dermatitis in dogs	[210]
Peppermint	*Mentha piperita*	*Lamiaceae*	contact allergy, pseudoallergy, stomatitis	[33, 34, 93, 118, 211–215]
Poppy seed (opium p., garden p.)	*Papaver somniferum*	*Papaveraceae*	immediate type reactions, (food-dependent, exercise-induced) anaphylaxis	[46, 48, 49, 216–221]
Rosemary (old man)	*Rosmarinus officinalis*	*Lamiaceae*	asthma, contact dermatitis	[39, 96, 222]
Saffron	*Crocus sativus*	*Iridaceae*	anaphylaxis, asthma, rhinoconjunctivitis	[6, 10, 26, 223]
Sage	*Salvia officinalis*	*Lamiaceae*	contact dermatitis, respiratory symptoms	[85, 93, 224–226]
Savory	*Satureja hortensis*	*Lamiaceae*	asthma	[96]
Sesame seed (gingelly, semsem, benne)	*Sesamum indicum*	*Pedaliaceae*	anaphylaxis, asthma, rhinitis, urticaria	[18, 24, 37, 49, 74, 80, 227–246]

Table 1 (continued)

Spices (synonyms)	Species	Family	Reported symptoms	Allergy reports
Star anise (Indian A., Chinese A., Badian A.)	*Illicium verum*	*Illiaceae*	contact dermatitis	[36, 247]
Tarragon	*Artemisia dracunculus*	*Asteraceae*	subglottic edema	[248]
Thyme (garden thyme)	*Thymus vulgaris*	*Lamiaceae*	asthma, systemic, reactions, eczema	[93, 96, 161, 249]
Turmeric (Indian saffron)	*Curcuma longa*	*Zingiberaceae*	contact dermatitis, asthma	[85, 223, 250–253]
Vanilla	*Vanilla planifolia*	*Orchidaceae*	atopic dermatitis, contact dermatitis	[8, 38, 119–121, 254, 255]

symptoms, taking vanilla as a paradigm [8]. No data are available today on the possible outgrowth of spice allergy, as no follow-up studies have been performed so far. Sensitization to spices is directly dependent on the number of possible contact events. Therefore, in adult patients spice allergy (e.g. pepper, saffron, fennel, anise or paprika) is especially seen in occupational settings, for instance in bakers, butchers, florists or spice factory workers [9–20]. Mainly inhalation or skin contact play a role for sensitization [21, 22]. On the other hand, only very low doses are necessary to elicit symptoms ranging from skin reactions after direct spice contact, food-associated symptoms after ingestion, to asthma after inhaling the dust of spices (table 1). Several cases of anaphylaxis to spices from different plant families (e.g. mustard, saffron, anise) have been reported as well [18, 23–30]. Besides IgE-mediated reactions also type IV hypersensitivities may occur as a consequence of exposure [31, 32], sometimes difficult to diagnose due to irritating components in spices.

Considering the low amounts of spices that are used for flavouring of foods, it is expected that the thresholds of sensitization and triggering of symptoms may be very low. However, the panel on dietetic products, nutrition and allergies (NDA) of the European Food Safety Authority (EFSA) stated in a press release from 25 March 2004 that the current scientific evidence is insufficient to establish an intake threshold for any of the spices included in the food allergen list (celery, mustard, sesame), below which an allergic reaction does not occur (www.efsa.eu.int/science/nda/catindex_en.html). Also, thresholds for the huge number of other spices are a complete black box today.

For allergic patients it is furthermore important to realize that spices can also occur as additives and ingredients in compositions other than food. For example, peppermint or cinnamon oil are used to flavour toothpaste or are applied in dental care and have been shown to induce contact allergy [33, 34]. Other sources may be massage oils, which contain oil of cinnamon and cloves [35], and many cosmetics or essential oils are derived from 'spicy' sources, for instance star anise [36], sesame seed [37], vanilla [38] or rosemary [39]. In addition, it has been noted that patients allergic to Peru balsam or fragrance mix often show reactions to spices and flavorings such as cinnamon, vanilla, cloves, curry, allspice, anise and ginger [40, 41].

Biological Effects of Spices: Hot, Medium Hot or Very Hot

Some hot spices as pepper (Piperaceae) and paprika, cayenne or chilli *(Capsicum annuum)* contain pharmacologically active substances, which are tasty but act on the barrier function of epithelia [42]. Piperine in black pepper, for example, seems to inhibit paracellular transport by producing cellular swellings. On the contrary, some hot spices may support their own paracellular transport across an intestinal epithelial layer via substances like capsaicin (paprika, chilli, cayenne pepper). From our studies we conclude that the hotter spices are, the more likely they could act as adjuvants for sensitization by promoting a transport of molecules below a molecular mass of 70 kDa. This molecular size corresponds to the size of molecules, which are relevant for sensitization and IgE binding in spice allergy. Moreover, plants may contain detergent substances like saponin, which also affect the epithelial barrier [43].

Table 2. Reported IgE reactivities to molecules or extracts of spices.

	Bet v 1 homologues	Profilin homologues	Lipid transferases	Seed storage proteins (11S or 2S albumins, germins)	IgE reactivities to other molecules (kDa) or extracts	References
Allspice						
Anise	+ (Pim a 1)	+ (Pim a 2)			12, 20, 33, 34, 35, 37, 39, 40, 42, 48, 50–70 kDa	[12, 47, 87]
Basil					skin prick tests, CAP system	[91, 93]
Bay leaf					skin prick tests, RAST	[94, 96]
Caraway seed					20, 33, 34, 37, 39, 42, 48 kDa	[12]
Cardamom					skin prick tests, scratch tests	[17, 97]
Cayenne					skin prick tests, scratch tests, RAST	[82, 83, 96]
Celery	+ (Api g 1)	+ (Api g 4)			30–70 kDa, including 55/58 kDa (Api g 5)	[56, 98–100]
Chervil					–	
Chilli powder						
Chives					RAST, skin prick tests	[104]
Cinnamon						
Cloves						
Coriander	+ (Cor s 1)	+ (Cor s 2)			12, 20, 21, 33, 34, 35, 37, 39, 40, 42, 48, ~ 70 kDa	[12, 47, 87]
Cumin seeds	+ (Cum c 1)	+ (Cum c 2)			20, 33, 34, 37, 39, 42, 48, ~70 kDa	[12, 47]
Dill					12, 21, 35, 40 kDa	[87]
Fennel	+ (Foe v 1)	+ (Foe v 2)			20, 33, 34, 37, 39, 42, 48, 50–70, 65, 75 kDa	[12, 20, 47]
Garlic					10, 12, 20, 31–60, 40, 42, 54, 56 kDa (alliin lyase)	[20, 150, 151, 153, 159]
Ginger					14, 23, 34 kDa	[87]
Jalapeno pepper						
Lovage					–	
Marjoram					skin tests, RAST	[93]
Mustard				14 kDa (Bra j 1, Sin a 1)		[76, 174, 256]
Nutmeg and mace					skin prick tests, scratch tests, RAST, histamine release tests	[22, 62, 63, 69, 96]
Onion			15 kDa		12, 43 kDa	[153, 193]
Oregano					RAST, skin prick tests	[93, 96]
Paprika	+	+ (Cap a 2)			10, 17, 23 (Cap a 1w = osmotin-like), 24, 28, 29, 30, 32, 36, 40, 46, 69 kDa	[70, 71, 125, 197]
Parsley	+ (Pet c 1)	+ (Pet c 2)				see figure 2
Pepper black, white, green					11.8, 13.6, 14, 25, 28 (GLP), 30, 35, 40, 60 kDa	[11, 44]
Peppermint					skin prick tests	[93, 118]
Poppy seed	+	+			5, 20, 25, 30, 34, 40, 45 kDa	[46]
Rosemary					skin prick tests, RAST	[96]
Saffron		+			21 kDa (Cro s 1)	[10], www.allergen.org/List.htm
Sage					skin prick tests	[93, 226]
Savory					skin prick tests	[96]
Sesame seed		+		7 (Ses i 2 2S), 9 kDa (Ses i 1 2S)	10, 12, 14, 15–20, 15 (Ses i 5, oleosin), 17 (Ses i 4, oleosin), 25, 29, 32, 34, 45 (Ses i 3, vicilin-type globulin), 45, 52, 30–67, 78 kDa, Ses i 4, Ses i 5	[74, 99, 234, 237, 239, 246], www.allergen.org/List.htm
Star anise						
Tarragon					28–46, 60 kDa in related mugwort *(Artemisia vulgaris)*	[225, 248]
Thyme					skin prick tests, RAST	[93, 96]
Turmeric						
Vanilla						

Spices without reported IgE reactivities are highlighted in grey.

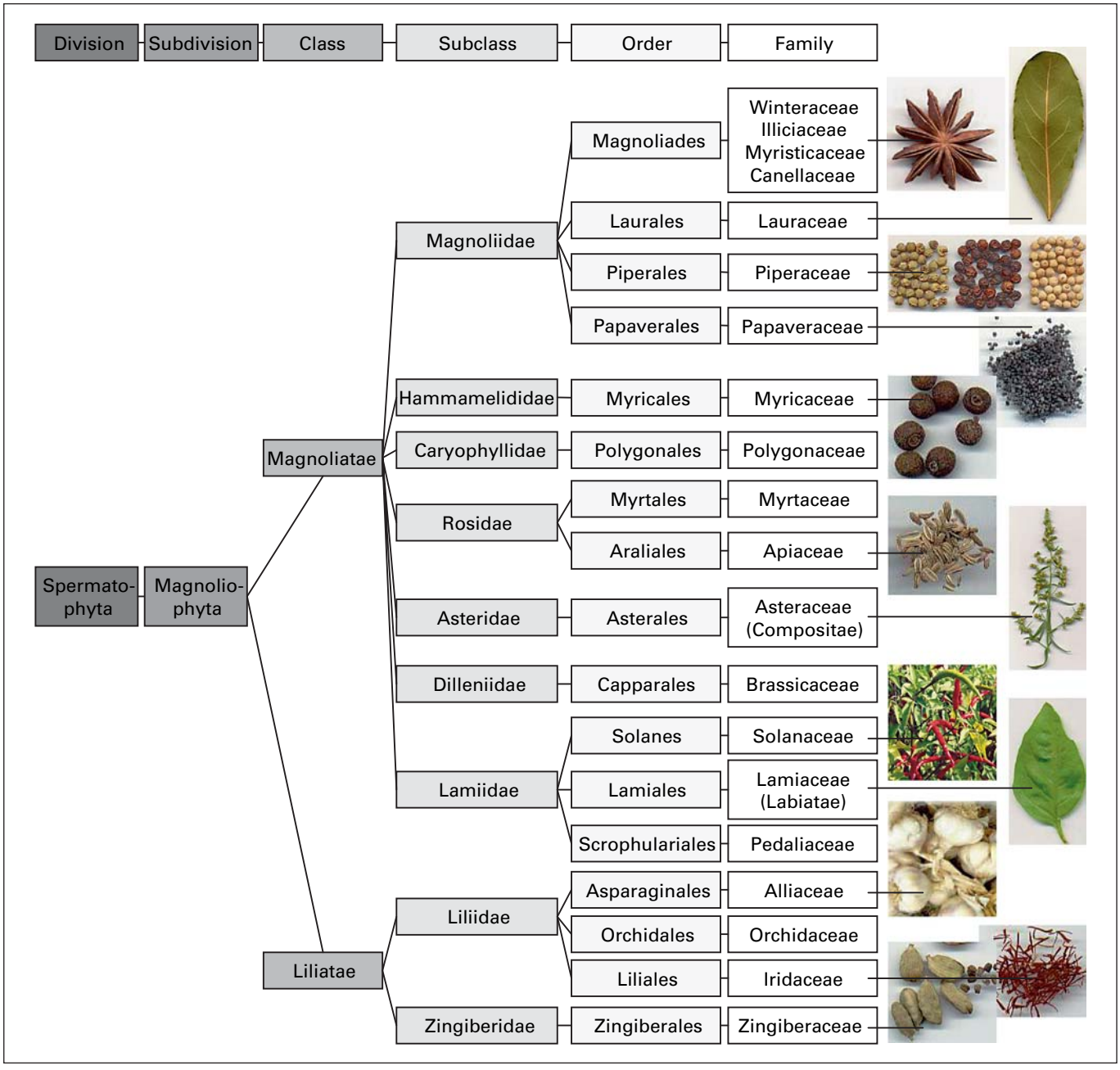

Fig. 1. Botanical relations of important spice families. Examples for respective families can be found in table 1 (photographs are used with the kind permission of Dr. Gernot Katzer, http://webdb.uni-graz.at/~katzer).

The Allergenicity of Spices Depends on the Grade and Type of Processing

Spices are used raw (e.g. parsley, lovage), or processed, for instance pickled (green pepper), dried (laurel, paprika, black pepper), toasted (sesame), roasted (poppy) or cooked (celery). Depending on the extent and type of processing, some of the spice allergens may be destroyed and loose their IgE-binding capacity, but enhancement of the binding capability is possible likewise. Especially hot spices as paprika, chilli or pepper are routinely processed by drying and grinding. This procedure obviously destroys Bet v 1

Table 3. Blends are composed of a variety of spices depending on the local manufacturer's recipe

Spice blends	Composed of
Bay seafood seasoning blend	Bay leaves, black pepper, cardamom, celery, cloves, ginger, mustard, nutmeg, paprika, pepper, salt
Cajun seasoning	Black pepper, chilli powder, garlic powder, nutmeg, onion powder, parsley flakes, red pepper (cayenne), salt
California style garlic blend	Cotton seed, garlic, parsley, soybean oil
Creole seasoning blend	Bay leaves, black pepper, chilli powder, garlic, onion, oregano, paprika, red pepper, salt, thyme
Curry powder	Cinnamon, cloves, coriander, cumin, nutmeg, onion, pepper corns, turmeric
Five-spice powder blend	Allspice, anise seed, cinnamon, cloves, fennel seed, ginger, pepper
Greek seasoning	Cinnamon, cornstarch, garlic, nutmeg, onion, oregano, parsley, pepper, salt
Ground seasoning blend	Celery seeds, onion powder, salt
Herbs seasoning blend	Basil, marjoram, oregano, parsley, rosemary, sage, thyme
Italian seasoning	Basil, coriander, marjoram, oregano, pepper, rosemary, sage, savory, thyme
Ketchup	Allspice, cinnamon, cloves, garlic, onion powder, sugar, tomatoes, vinegar
Ketchup, hot	Cider vinegar, garlic, jalapeno chilli, onions, oregano, salt, tomato paste, tomatoes
Lemon and pepper	Black pepper, celery seed, citric acid, corn starch, garlic powder, lemon oil, onion, salt, sugar
Poultry seasoning	Black pepper, cloves, marjoram, nutmeg, rosemary, sage, thyme
Season-all	Black pepper, celery seed, chilli pepper, coriander, garlic, nutmeg, onion, paprika, salt
Taco seasoning	Chilli powder, cornstarch, cumin, garlic, onion, oregano, red pepper, salt
Thai seasoning	Basil, chilli peppers, cinnamon, coriander, cumin, garlic, ginger, lemon peel, lime oil, paprika, red pepper, star anise, tomato, white pepper

homologues as well as profilins to a large extent, at least in the case of paprika [44], which is derived from bell peppers [45]. However, in paprika and the related chilli pepper we identified a 23-kDa allergen as a pathogenesis-related protein P23 (osmotin) by N-terminal sequencing, which resisted processing [44].

Also poppy seeds, which are used in the cuisine in roasted condition, and dried Apiaceae spices like anise, fennel, cumin or coriander, still contain antigenetically intact Bet v 1 and profilin homologues [46, 47]. They may even elicit anaphylaxis [27, 29, 48]. Poppy seeds share epitopes with sesame [49], which is usually dried only, but often gets toasted on bread.

The higher-molecular-weight molecules of spices of the Apiaceae and Solanaceae families expressing cross-reactive carbohydrate determinants [46, 50–52] seem to be more resistant to food processing including grinding, roasting and cooking, and retain the potential to induce clinical symptoms [44, 51]. Especially celery allergens are extremely heat stable [51]. After processing through drying and grinding, a germin-like protein (GLP) in dried black and pickled green pepper retained its capability of IgE binding [44].

Not only rigorous processing, but also freeze-drying may alter the allergenicity of spices. In a comparative study, some lyophilized spices produced even stronger skin prick test reactions than the corresponding whole spice extracts, but 5% produced weaker reactions or remained totally negative in some patients [53].

In the above-cited press release, the EFSA stated that no general effects of food processing on the allergenic potential of proteins can be predicted to date. This also seems to be true for spices.

Spices Cross-React with Inhalative Allergens and Other Food Allergens

In most cases of spice allergy, extensive serological and clinical cross-reactions with pollen were reported. Especially mugwort and birch pollen sensitization represent a risk to progress to spice allergy. The resulting cross-reactions are summarized in the celery-mugwort-spice syndrome [54–58], which later has been expanded to celery-birch-mugwort-spice syndrome [59], and to the celery-carrot-mugwort-condiment syndrome [60, 61]. Therefore,

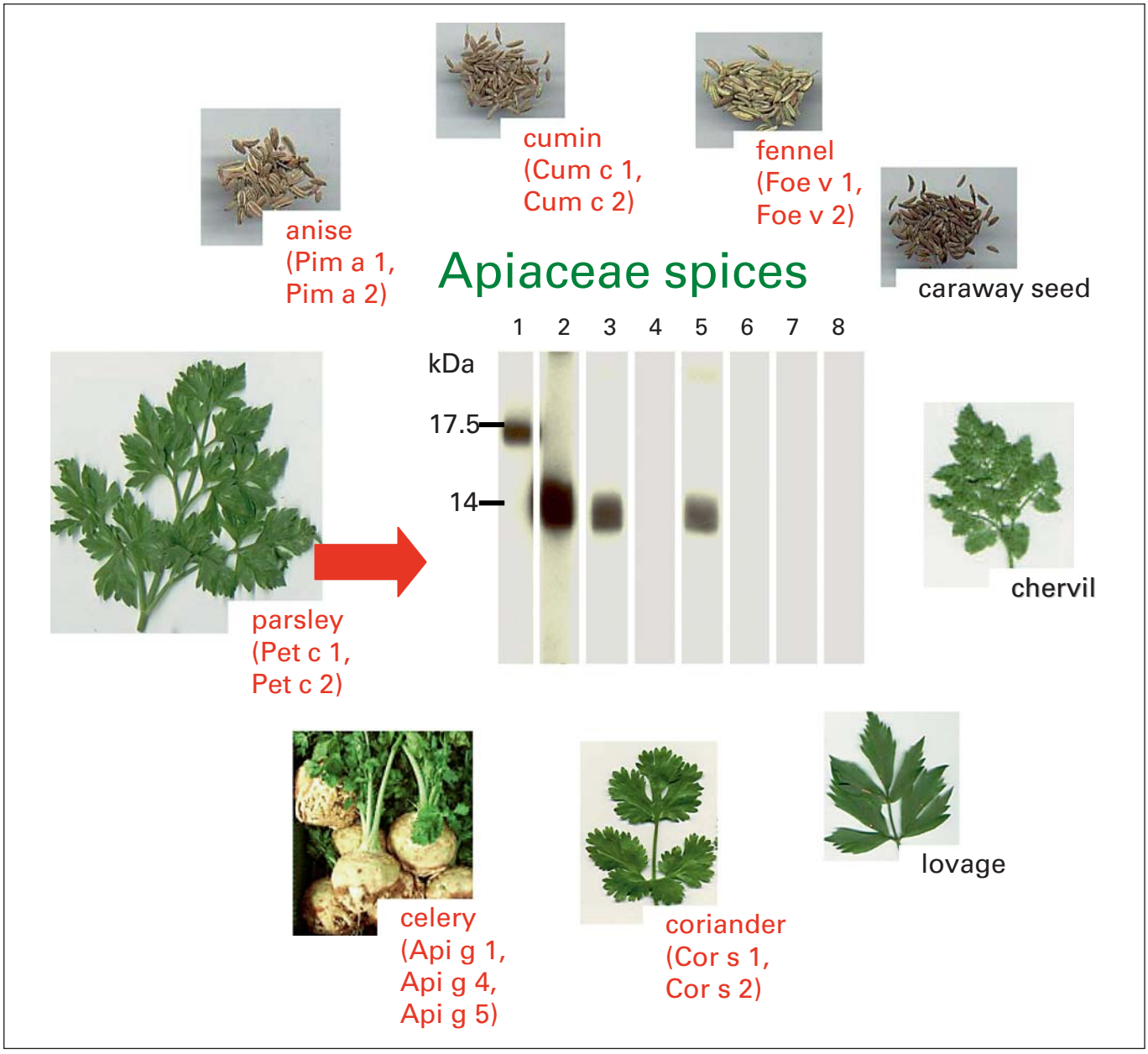

Fig. 2. Spices of the Apiaceae family with proven content of proteins homologous to Bet v 1 and profilin (names and allergenic molecules in red). As an example, blotted extract of parsley *(Petroselinum crispum)* was prepared. A monoclonal mouse antibody detected a Bet v 1 homologue (Pet c 1) at 17.5 kDa in parsley (1). A polyclonal rabbit antibody against profilin detected a profilin (Pet c 2) at 14 kDa (2). Serum of a patient with birch-mugwort-spice syndrome contained IgE to Pet c 2 (3), which could be inhibited by recombinant Bet v 2 (birch pollen profilin) (4), but not by control allergen Bet v 1 (5). The IgE anti-profilin reaction could further be completely inhibited by extracts of birch pollen (6), mugwort (7) or celery (8).

spice allergy is often explained as a secondary effect after a primary sensitization with inhalative allergens. In the beginnings of cross-reactivity studies, pollen extracts were often used for cross-inhibitions, for example in RAST [62, 63]. Later, recombinant allergens were applied for inhibitions and significantly increased our understanding of the molecular basis of the observed clinical IgE cross-reactivities [46, 47]. From these studies we have learned that the closer the plant producing the pollen is related to the spice, the more likely cross-reactions may

occur. This is due to the presence of conserved homologues in different plants. However, some molecules have such important functions in the plant cell that they are expressed even in distantly related plants. Among these molecules, profilin and Bet v 1 homologues seem to be responsible for many cross-reactivities [45, 50, 64]. They are very sensitive to gastric digestion [65, 66], therefore, inhalative sensitization is most likely the first event in patients allergic to these proteins, even though we have recently observed that gastric hypoacidity can favor sensitization to digestion-labile antigens as well [67]. Bet v 1 homologues have, for instance, been detected in the botanical family of Apiaceae, comprising celery, carrot, and many other popular spices, such as cumin, anise, fennel [47]. In figure 2 we show that parsley *(Petroselinum crispum),* a very popular Apiaceae spice, also contains a Bet v 1 homologue and a profilin, which should be termed Pet c 1 and Pet c 2, respectively, according to the international allergen nomenclature (www.allergen.org). The Bet v 1 homologous allergens in celery and carrot have already been cloned and designated Api g 1 and Dau c 1, respectively [68]. The high conservation of Bet v 1 homologues and profilins in the Apiaceae family may thus be an important cause of cross-reactions within the family, but also to pollen [4, 69].

Bell peppers are the origin of paprika, a spice widely used for flavouring food all over the world. They belong to the *Capsicum* genus and contain a profilin homologous protein, designated Cap a 2 [70]. Depending on the horticultural strain, their Bet v 1 homologue and their pathogenesis-related protein P23 may be either expressed (and relevant for IgE binding), or totally abolished [71]. Additionally, a case of cross-reactivity between bell pepper and latex allergens has been reported [72].

In black pepper, a germin-like protein has been identified as an allergen. The germins and GLP families belong to the Cupin superfamily [73] and have recently attracted interest as an allergen source due to their abundance in many food plants, probably including spices [52].

Another class of food allergens of well-recognized clinical importance is that of seed storage 2S albumins. They have been identified in most edible seeds and nuts, like e.g. in mustard, sesame and peanut, Brazil nut and walnut. Regarding spices, a strong correlation between IgE binding to these proteins and food-induced anaphylaxis has been demonstrated for sesame seeds [74].

Furthermore, it has to be kept in mind that ingredients of different spice blends (listed in table 3) can induce symptoms via cross-reactivity, for instance cotton seed (e.g. in California Style Garlic Blend) shows sequence homology to Jug r 1 and Jug r 2 from walnut [75, 76], and tomato (e.g. in ketchup) can also induce reactions in patients allergic to grass pollen [77].

In addition to cross-reactivities, there are single cases of spice allergens that obviously sensitize without detectable primary inhalative sensitization, for instance mustard [23, 25]. Also here, a seed storage 2S albumin may play a role as primary sensitizer [18], which is very resistant to gastrointestinal digestion and thus sensitizes via the intestinal mucosa. Mustard is a member of the Brassicaceae family, cross-reactions are known between the rapeseed allergen Bn III and the mustard allergen Sin a 1 [78].

In summary, the main allergens responsible for cross-reactivities are homologues of the birch pollen allergen Bet v 1 [47, 68], the panallergen profilin [10, 56, 64, 70, 79], and seed storage proteins as germins and GLPs [52, 74], or 2S albumins [80] (table 2). In addition, carbohydrate determinants can evoke cross-reactions as well [81]. Hypersensitivity reactions mediated by IgE were observed most frequently in the botanical families: Apiaceae > Solanaceae > Lamiaceae > Asteraceae > Papaveraceae > Brassicaceae, and to a lower extent in Piperaceae, Myrtaceae, Myricaceaea, Orchidaceae, Lauraceaea, Zingiberaceae, and Alliaceae. The botanical relations between these families are depicted in figure 1.

Diagnostic Procedures: IgE, Skin Prick Tests, Challenges

The procedures for diagnosing spice allergy comprise a careful anamnesis and various techniques of skin testing, whereas RAST can be negative in more than half of the cases. A combination of these procedures may be useful [82], and allowed the diagnosis of type I spice allergy in 16.6% of the patients referred to a Swiss clinic for food-allergic symptoms [5]. Furthermore, in the same study skin prick tests with native spices and spice extracts rendered comparable results. This confirms that fresh spices can also be used for prick-to-prick tests in cases where extracts are not commercially available. Scratch tests may be helpful as well [69, 83]. For double-blind placebo-controlled food challenge, powdered spices can be used when entrapped in capsules. In addition, specific bronchial inhalation challenges [14], or in rare cases, anterior rhinomanometry, as shown for garlic and onion [84], have been performed, although they are of less practical value and expensive. Further, a test system using patients' leucocytes and measuring the histamine

Table 4. Related internet pages with information about allergens and spices

Information	Internet address
Detailed information about spices	http://webdb.uni-graz.at/~katzer/germ
Spice encyclopedia	http://www.spiceadvice.com/encyclopedia/index.html
Recipes of spice blends	http://www.online-cookbook.com/goto/cook/tcbr
EU directive	http://www.europar/.eu.int/commonpositions/2003/pdf/c5-0080-03_en.pdf
Official list of allergens	http://www.allergen.org/List.htm
Allergen nomenclature	http://www.expasy.org/cgi-bin/lists?allergen.txt http://www.allergen.org/Pub.htm
Allergen sequence database at BISF	http://www.iit.edu/~sgendel/fa.htm
Database of allergenic molecules	http://www.allergome.org/
Structural database of allergenic proteins	http://fermi.utmb.edu/SDAP/

release after incubation with various spices was described [62].

For delayed-type reactions, skin tests may not be sufficiently reliable: only 3 of 55 patients exhibited relevant patch test responses to spices [85]. These tests therefore have to be improved or confirmed by other test methods [31, 86].

Labelling as Prevention Strategy

Prevention or avoidance is the main therapeutic concept in inhalative, orally provoked or contact spice allergy, as no causative treatment is known at present. Treatment of cross-reactive pollen allergy, for example by specific immunotherapy, may have a positive effect on concomitant spice allergy. However, at present, no such study has been performed.

A major obstacle to avoidance strategies is the fact that many spices are hidden in prepared or pre-packed food due to the mystified secrets of the cuisine or the producer. In addition, spice blends containing numerous different flavourings (table 3) represent a special challenge for the allergic patients. Generally, all components of a prepacked food should be listed in descending order of weight preceded by the word 'ingredients'. The 1978 regulations (Council Directive 2000/13/EC of 18 December 1978) specified that in a mixture of spices or herbs, where no particular one dominates, the list should be accompanied by an expression like 'in variable proportion', and that fresh fruits and vegetables (including spices) do not even require a list of ingredients. At that time, it was further sufficient to designate these ingredients by the name of the category 'spice(s)' or 'mixed spices', if they represented less than 2% of the weight of the foodstuff. Recognizing that the imprecise labelling policy for foods might be life-threatening for the allergic patient, a defined list of foods with allergenic potential has been taken up in the EU labelling issues in 2004. The obligatory list of ingredients contains the spices celery, mustard and sesame seed. The Directive 2003/89/EC of the European Parliament and Council amending Directive 2000/13, adopted on 10 November 2003 (OJ L308 of 25.11.2003), will become effective by 25 November 2004. It indicates that all ingredients should appear on the label, regardless of the quantity contained in the finished food. This means that exceptions, e.g. the option to declare certain ingredients by category (see above), will no longer apply to the most common food allergens including spices listed in Annex IIIa of the Directive 2003/89/EC. This is an important step towards the prevention of symptoms in spice-allergic patients. In addition, special care should be taken to unitize the nomenclature for labels to clearly indicate the contents, for instance the term pepper is often used for spices from either the family Piperaceae (pepper) or Solanaceae (paprika, sweet pepper, bell pepper). For the future, it would even be preferable if companies could guarantee that their products are free of certain ingredients (like spices), and therefore are also suitable for allergic patients.

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